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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,090	EICHEN ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,18-20,22-26,28,35-39,41,43,44,47-51,53-57,60-63 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,18-20,22-26,28,35-39,41,43,44,47-51,53-57,60-63 and 65* is/are rejected.

7)☒ Claim(s) *20,33,35 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/28/09; 5/14/03; 6/3/03*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 28, 2009 has been entered.

Status of the Application

2. Claims 1, 4-9, 18-20, 22-26, 28, 35-39, 41, 43, 44, 47-51, 53-57, 60-63, and 65 are currently pending. In the response filed on October 28, 2009, Applicant amended claims 1, 18-20, 22-26, 28, 35-39, 41, 44, 47-51 and 65. Claims 27 and 46 were canceled.

It is noted that the application has been re-assigned to Examiner Angela Bertagna. The Examiner's correspondence information is provided at the conclusion of the Office Action.

The following include new grounds of rejection necessitated by Applicant's amendments to the claims. Any previously made rejections not reiterated below have been withdrawn as being obviated by the amendment. Applicant's arguments filed on October 28, 2009 that remain pertinent to the new grounds of rejection above have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on October 28, 2009 is acknowledged. A signed copy is enclosed. The following foreign patent documents listed on the IDS have been cited on a previously submitted IDS and considered by the Examiner: EP 0364208, EP 0444840, WO 90/05300, and WO 97/44651. These duplicate citations have been lined through.

A corrected version of the IDS submitted on May 14, 2003 is also enclosed. The citation of the non-patent literature document authored by Size has been corrected to include the correct publication date of the reference.

A corrected version of the IDS filed on June 3, 2003 is also enclosed. The citation of the non-patent literature document authored by Seeman has been corrected to include the correct publication date of the reference.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(4), because reference character "**102**" has been used to designate both "an assay device" (see Figure 1A) and "an electrode" (see Figure 3A). Also, reference character "**196**" has been used to designate both "an assay set" and "an electrode" (see Figure 3D), and reference character "**244**" has been used to designate both "an assay set" and "a target nucleic acid sequence" (see page 27). Furthermore, reference character **410** has been used to designate both "DNA" and "a path" (see page 32 and Figure 12). Also, reference characters **122**, **124**, **126**, and **132** have each been used to designate two different parts (compare Figures 2 and 15). Also, reference characters **502**, **504**, **506**, and **508** have each been used to designate two different parts (compare Figure 13 and page 33 with Figure 21 and page 46, where: (i) reference character **502** has been used to designate "a recognition moiety" and "electrodes", (ii) reference character **504** has been used to designate "a recognition moiety" and "a target oligonucleotide", (iii) reference character **506** has been used to designate "a recognition moiety" and "a 3'-deoxy site", and (iv) reference character **508** has been used to designate "a recognition moiety" and "DNA molecules pendant with gold colloids"). Also, reference character **708** has been used to designate both "nucleic acids derivatized with carboxyalkyl groups" (see page 53 and Figure 23) and "a gap" (see Figure 24). Finally, reference character **1010** has been used to designate both "a base" (see Figures 35-36 and page 61) and also "a reservoir" (see Figure 37 and page 62). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet

submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are also objected to as failing to comply with 37 CFR 1.84(p)(5), because they do not include the following reference sign(s) mentioned in the description: **162**, **164**, **168,** and **192** (see page 26); **256** (see page 27); and **718** (see page 53). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The drawings are also objected to as failing to comply with 37 CFR 1.84(p)(5), because they include the following reference character(s) not mentioned in the description: **100** (see Figure 3A), **243** (see Figure 4B), and **120** (see Figure 15). Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if

only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

6. (A) Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it includes the legal phraseology "said". Correction is required. See MPEP § 608.01(b).

(B) The disclosure is also objected to because of the following informalities: The drawings show Figures 1A-1B and 2A-2D, but the "Brief Description of the Drawings" section

only refers to "Figure 1" and "Figure 2". As noted in MPEP 608.01(f), "[I]f the drawings show Figures 1A, 1B, and 1C and the brief description of the drawings refers only to Figure 1, the examiner should object to the brief description, and require applicant to provide a brief description of Figures 1A, 1B, and 1C.

Appropriate correction is required.

Claim Interpretation

7. The "means for determining whether the one or more targets are in the sample as a result of the extent of electric conductance between the two electrodes of each assay set" in claims 1, 35, and 37 has been treated under 35 U.S.C. 112, sixth paragraph.

Claim Objections

8. Claims 20 and 39 are objected to because of the following informalities: These claims recite incorrect status identifiers.

Claim 23 is objected to because of the following informalities: This claim appears to contain a typographical error in line 2, where "antibody fraction" is recited. It would appear that "antibody fragment" was intended.

Claim 35 is objected to because of the following informalities: This claim contains two periods - one at the end of line 29 and another at the end of line 32.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 25, 26, 28, 37, 50, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Mroczkowski et al. (WO 90/05300 A1; cited previously).

These claims are drawn to methods for detecting the presence of one or more targets in a sample based on an observed change in electric conductance resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes.

Mroczkowski teaches methods and systems for detecting the presence of targets in a sample based on the measurement of an electrical signal generated between two electrodes (see abstract, Figures 1-2, and page 3, lines 2-27).

Regarding claims 25, 26, and 28, Mroczkowski teaches a method for detecting the presence of one or more biological molecule targets in a sample comprising:

(a) reacting a sample, which may or may not have at least one of the biological molecule targets with a first reagent solution to bind nucleation center-forming entities to the one or more biological targets (see page 10, lines 7-18 and page 10, lines 24-36, where the conductively-labeled antibodies are the nucleation center-forming entities; page 14, lines 3-12, page 18, lines 28-31, and page 20, lines 11-33, for example, teach that the conductive label may be gold particles, which are a nucleation center-forming entity),

(b) providing an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety that is capable of specifically binding to one of the one or more biological molecule targets, positioned in the gap, and bound to the substrate (see page 10, lines 7-12 and lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(c) contacting the assay device with the sample under conditions that permit the formation of complexes between the biological molecule target and the recognition moiety (page 10, lines 7-18 and lines 24-36),

(d) contacting the assay device with a second reagent that includes metal ions and a reducing agent to deposit metal on the complexes formed in step (c) if one or more of the nucleation center-forming entities is present, whereby the deposited metal forms a conducting metal layer over the nucleation center-forming entities and a conductive bridge between the two electrodes (see page 10, lines 7-23 and page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated antibodies; page 25, lines 13-29 provides further details of the silver enhancement process),

(e) connecting the electrodes to an electric or electronic module and measuring the conductance between the two electrodes, wherein a conductance measurement above a threshold conductance value indicates the presence of a biological molecule target in the sample, whereas a conductance measurement below or at the threshold conductance value indicates the absence of

the biological molecule target in the sample (see page 10, lines 7-23 and page 10, line 24 – page 11, line 5, where the resistance measurements conducted with an ohmmeter provide an indirect measure of the conductance, which is reciprocal ohms; see also page 17, line 33 - page 18, line 8, and page 23 for additional details of the resistance measurements conducted by Mroczkowski).

Further regarding claims 25, 26, and 28, as evidenced by the specification of the instant application at page 42, the acidic solution of silver ions and hydroquinone taught by Mroczkowski at page 25, lines 13-29, for example, is metastable, which results in metal deposition only occurring when a nucleation center-forming entity is present.

Further regarding claims 26 and 28, the nucleation center-forming entities of Mroczkowski (*i.e.* the gold-labeled antibodies) can also bind monomers of a conductive polymer, since the gold component of the gold-labeled antibodies interacts (binds) with the silver ions (*i.e.* the monomers recited in claims 26 and 28) added in the silver enhancement step. Since the silver enhancement step described in Mroczkowski results in the production of a conductive layer of aggregated silver atop the gold-labeled antibodies that bridges the gap between the two electrodes (see page 18-19, for example), the silver ions used in the silver enhancement step are monomers of a conductive polymer that are capable of being bound by the gold component of the nucleation center-forming entities. Thus, the silver enhancement step of Mroczkowski comprises: (i) contacting the complexes formed between the biological molecule targets and the substrate-immobilized recognition moiety with a reagent solution comprising monomers of a conductive polymer, such that the monomers can bind to the nucleation center-forming entities, and (ii) treating the assay device such that the monomers will polymerize to form a conductive polymer that bridges the gap between the two electrodes as required by claims 26 and 28.

Regarding claim 37, Mroczkowski teaches a microelectronic device having a plurality of layers, with a first group of conductors being defined as stripes in a one or more first layers and a second group of conductors being defined as stripes in one or more second layers of the device with each of said second layers being separated from a first layer by a non-conductive substance, and wherein electrodes are formed as open ends of the conductors by openings or cut-outs in a vertical direction through the layers (see Figures 6 and 8 and the accompanying descriptions at page 12, lines 1-33 and page 17, lines 4-32; see also pages 21-22). In the device of Mroczkowski, each pair of electrodes forms part of an assay set, which has a recognition moiety for binding to a component of a cellular target selected from the group consisting of a bacterium, a virus, and a cell (see page 5, lines 6-10 and page 10, lines 7-36). The electronic device of Mroczkowski also comprises a means for determining whether the one or more targets is present in the sample as a result of the extent of electric conductance between each pair of electrodes in each assay set (see page 17, line 33 – page 18, line 8, where the ohmmeter provides via the obtained resistance measurements an indirect measure of conductance, which is reciprocal ohms). Finally, the assay sets in the device of Mroczkowski are adapted to accept reagents formulated to deposit a conductive substance onto a complex formed between a recognition moiety and a component of the cellular target (see pages 10 and 17, as discussed in greater detail above). It is noted that the limitations recited in lines 13-20 of the claim only require the electronic device to be **capable of** accepting the recited reagents and do **not** require the presence of the particular reagents recited in lines 13-20 of the claim to be present in the device. Since the device of Mroczkowski is designed to receive reagents (see page 10, for example), it is inherently adapted to receive the reagents described in lines 13-20 of claim 37.

Regarding claims 50 and 51, the antibodies detected in the above method described by Mroczkowski are components of a cell. Also, Mroczkowski teaches that the disclosed methods can be used to detect other cell components at page 5, lines 5-10.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 4-7, 18-20, 22-24, 43, 44, 47-49, 54, 55, 57, 62, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously).

Claims 1, 4-9, 18-20, 22, 23, 43, 44, and 57 and 65 are drawn to a system for detecting the presence of a target selected from the group consisting of a bacterium, a cell, or a virus in a

sample that comprises a substrate upon which two electrodes are attached, a recognition moiety that binds to a component of the target immobilized on the substrate between the electrodes, and nucleation center-forming entities that bind to the target or a component of the target. Claims 24 and 49 are drawn to a method for detecting the presence of one or more target nucleic acids in a sample based on an observed change in electric conductance resulting from the target nucleic acid binding to an oligonucleotide recognition moiety immobilized to a substrate between two electrodes. Claims 54 and 62 further limit the structure of the device of claim 37. Claims 47 and 48 are drawn to the methods of claims 25 and 26, respectively, wherein the one or more biological molecule targets are nucleic acids and the recognition moieties are oligonucleotides.

Mroczkowski teaches methods and systems for detecting the presence of targets in a sample based on the measurement of an electrical signal generated between two electrodes (see abstract, Figures 1-2, and page 3, lines 2-27). As discussed above, the teachings of Mroczkowski anticipate the methods of claims 25, 26, 28, 50, and 51 and the device of claim 37.

Regarding claims 1, 57, and 65, Mroczkowski teaches a system for detecting the presence of one or more targets in a sample that comprises:

(a) an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety, that is capable of specifically binding to a component of one of the one or more targets, positioned in the gap, and bound to the substrate (see page 10, lines 7-12 and lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(b) an electric or electronic module arranged and configured to measure electric conductance between the at least two electrodes of the one or more assay sets (see page 17, line 33 - page 18, line 8 and page 23, where the ohmmeter measures electric conductance (*i.e.* reciprocal ohms) indirectly via the measurement of ohms of resistance),

(c) a sample that may or may not contain the target (page 10, lines 7-18 and lines 24-36),

(d) reagents comprising nucleation center-forming entities that bind to a component of the one or more biological targets (see page 10, lines 7-18 and page 10, lines 24-36, where the conductively-labeled antibodies are the nucleation center-forming entities; page 14, lines 3-12, page 18, lines 28-31, and page 20, lines 11-33, for example, teach that the conductive label may be gold particles, which are a nucleation center-forming entity),

(e) reagents comprising metal ions and a reducing agent (see page 10, lines 7-23 and page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated antibodies; page 25, lines 13-29 provides further details of the silver enhancement process), and

(f) means for determining whether at least one of the one or more targets are in the sample as a result of the extent of electric conductance between the two electrodes in each assay set (see page 17, line 33 - page 18, line 8 and page 23, where the ohmmeter, which measures electric conductance (*i.e.* reciprocal ohms) indirectly via the measurement of ohms of resistance, constitutes the claimed means).

Further regarding claims 1 and 65, the system of Mroczkowski is adapted to allow combination of the one or more assay sets, the sample, and the reagents. Also, in use, the recognition moieties in the system of Mroczkowski bind to a component of the target to form a

complex that is bound by the nucleation center-forming entities (see above, especially page 10). As noted above (see pages 18 and 25), the complex formation step is followed by a silver enhancement step in which the metal ions and reducing agent are used to deposit silver upon the nucleation center-forming entities (*i.e.* the gold particles) to form a conductive silver bridge between each pair of electrodes. Further, as evidenced by the specification of the instant application at page 42, the acidic solution of silver ions and hydroquinone taught by Mroczkowski at page 25, lines 13-29, for example, is metastable, which results in metal deposition only occurring when a nucleation center-forming entity is present.

Further regarding claim 65, Mroczkowski also teaches that the recognition moiety, which may be an antibody capable of specifically binding to an epitope of a cellular target can be attached to each of the two electrodes (page 12, lines 1-11, page 14, lines 3-15, and page 10, lines 7-23).

Regarding claims 4 and 6, Mroczkowski teaches that the nucleation center-forming entities are colloidal gold particles (see page 20, for example).

Regarding claims 5 and 7, Mroczkowski teaches that the nucleation center-forming entities are metal complexes, specifically gold complexes or platinum complexes (see, for example, page 14, lines 26-30).

Regarding claims 18-20, the system of Mroczkowski comprises a plurality of assay sets (see Figure 8 and page 17, lines 4-32). Mroczkowski further teaches that the recognition moiety in each assay set may be the same or different between assay sites to permit binding to the same or different targets (page 17, lines 8-12).

Regarding claims 22 and 23, Mroczkowski teaches that the component of the target bound by the recognition moiety is a protein or polypeptide, and that the recognition moiety is an antibody (see, for example, page 10, lines 7-22, for example).

Regarding claim 24, Mroczkowski teaches a method for detecting the presence of one or more biological molecule targets in a sample comprising:

(a) providing an assay device having one or more assay sets, wherein each of the assay sets comprises at least two electrodes positioned on a substrate and separated by a gap and a recognition moiety that is capable of specifically binding to one of the one or more biological molecule targets, positioned in the gap, and bound to the substrate (see page 10, lines 7-12 and lines 24-29; see also page 3, lines 1-37, page 12, lines 1-23, page 17, lines 4-32, and Figures 1, 2, and 8, which provides further details regarding the "diagnostic element" referenced at page 10 of Mroczkowski, which corresponds to the claimed assay device having one or more assay sets),

(b) contacting the assay device with the sample under conditions that permit the formation of complexes between the biological molecule target and the recognition moiety (page 10, lines 7-18 and lines 24-36),

(c) contacting the assay device with a first reagent solution to bind nucleation center-forming entities to the one or more biological targets complexed with the recognition moiety (see page 10, lines 7-18 and page 10, lines 24-36, where the conductively-labeled antibodies are the nucleation center-forming entities; page 14, lines 3-12, page 18, lines 28-31, and page 20, lines 11-33, for example, teach that the conductive label may be gold particles, which are a nucleation center-forming entity),

(d) contacting the assay device with a second reagent that includes metal ions and a reducing agent to deposit metal on the complexes formed in step (c) if one or more of the nucleation center-forming entities is present, whereby the deposited metal forms a conducting metal layer over the nucleation center-forming entities and a conductive bridge between the two electrodes (see page 10, lines 7-23 and page 10, line 24 - page 11, line 5; see also page 15, lines 9-19, page 18, lines 21-31, where Mroczkowski teaches silver enhancement of gold particles, such as gold-conjugated antibodies; page 25, lines 13-29 provides further details of the silver enhancement process), and

(e) connecting the electrodes to an electric or electronic module and measuring the conductance between the two electrodes, wherein a conductance measurement above a threshold conductance value indicates the presence of a biological molecule target in the sample, whereas a conductance measurement below or at the threshold conductance value indicates the absence of the biological molecule target in the sample (see page 10, lines 7-23 and page 10, line 24 – page 11, line 5, where the resistance measurements conducted with an ohmmeter provide an indirect measure of the conductance, which is reciprocal ohms; see also page 17, line 33 - page 18, line 8, and page 23 for additional details of the resistance measurements conducted by Mroczkowski).

Further regarding claim 24, as evidenced by the specification of the instant application at page 42, the acidic solution of silver ions and hydroquinone taught by Mroczkowski at page 25, lines 13-29, for example, is metastable, which results in metal deposition only occurring when a nucleation center-forming entity is present.

Regarding claim 49, the antibodies detected in the above method described by Mroczkowski are components of a cell. Also, Mroczkowski teaches that the disclosed methods can be used to detect other cell components at page 5, lines 5-10.

Mroczkowski does not teach that the nucleation center-forming entities bind to cells, bacteria, or viruses, as required by claim 1, from which claims 4-9, 18-20, 22, 23, 43, 44, 55, and 57 depend. Mroczkowski also does not teach applying the disclosed methods and devices to the detection of nucleic acid targets using oligonucleotide recognition moieties, as required by claims 24, 43, 44, 47-49, and 54. Finally, Mroczkowski does not teach the use of a computer as the means for determining the presence of the target in the sample as required by claims 55, 56, 62, and 65.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see abstract, Figure 4, Figure 22, and column 2, lines 25-52).

Regarding claims 1, 57, and 65, the system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37,

column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22).

Further regarding claim 1 and also regarding claims 43, 44, 47-49, and 54, Hollis further teaches that the target biological detected using the disclosed system and methods may be a cell, protein, or nucleic acid (see column 4, lines 21-25 and lines 41-45 and Table III at column 18). The nucleic acids detected by Hollis include nucleic acids that are a component of a cell or virus (see, for example, column 16, line 35 - column 17, line 67). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection (column 16, lines 35-42)." Also, in the embodiments comprising cell or nucleic acid detection, Hollis teaches that the recognition moiety is a molecule, such as a protein or antibody that binds to a component of the cell or a complementary oligonucleotide, respectively (see, for example, Table III at column 18).

Further regarding claim 65 and also regarding claim 55, Hollis teaches that "[T]he measurement process can be automated via on-chip microprocessor control to provide a very fast method of accessing each test site in the array (column 20, lines 14-16)."

Regarding claims 18-20, the system of Hollis comprises a plurality of assay sets (column 4, lines 15-49, for example). Hollis further teaches that the recognition moiety in each assay set may be capable of binding to the same type of cell component and also that the recognition moieties differ between assay sets to permit binding to different targets (see column 4, lines 36-49, for example).

Regarding claims 22 and 23, Hollis teaches that the component of the target bound by the recognition moiety is a protein or polypeptide, and that the recognition moiety is an antibody (see, for example, Table III at column 18).

Regarding claim 24, Hollis a method for using the disclosed system to detect nucleic acids that comprises adding a sample to the disclosed system to permit hybridization of any target nucleic acids in the sample with the substrate-immobilized oligonucleotide probes and detecting a change in the electrical conductance between the two electrodes bracketing each test site in the substrate containing immobilized oligonucleotide probes, thereby detecting the presence of the target nucleic acid in the sample (see, for example, column 4, lines 15-67, column 6, lines 35-65, column 7, lines – column 7, lines 20-37).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Hollis with those of Mroczkowski. In particular, an ordinary artisan would have been motivated by the teachings of Hollis to adapt the systems, devices, and methods of Mroczkowski to the detection of any biological target, such as cells or nucleic acids, in order to maximize the number of useful applications of the method. Since Hollis taught that nucleic acid detection and cell detection could be used in numerous useful applications (column 16, lines 35-42 and column 19, lines 5-15), an ordinary artisan would have been motivated to adapt the device suggested by the combined teachings of Mroczkowski and Olsen to the detection of these useful biological targets in order to further increase the number of useful applications of the system. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target and since Hollis taught that cells and nucleic acids were suitable targets for

detection via electrical methods. It also would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate a computer as the means for determining the presence of a target in a sample in the systems and devices of Mroczkowski. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Hollis taught that the electrical measurements in a similar system could be conducted using a computer to result in a rapid and automated detection step (column 20, lines 14-16). Thus, the system of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65, the device of claims 54 and 63, and the methods of claims 24 and 47-49 are *prima facie* obvious over Mroczkowski in view of Hollis.

13. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Kidwell et al. (US 5,384,265; newly cited) and further in view of Houthoff et al. (US 5,714,327; newly cited).

Claim 8 is drawn to the system of claim 4, wherein the colloid particles that comprise the nucleation center-forming entity are colloidal platinum particles.

As discussed above, the combined teachings of Mroczkowski and Hollis render obvious the system of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65 and the methods of claims 24 and 47-49.

Mroczkowski teaches the use of colloidal gold particles (page 20, for example) and also platinum complexes may be used as the nucleation center-forming entity (see page 14, lines 26-30 and page 20, for example).

However, neither Mroczkowski nor Hollis teaches the use of colloidal platinum as the nucleation center-forming entity as required by claim 8. Also, neither Mroczkowski nor Hollis suggests the use of platinum as the nucleation center-forming entity in a system together with the reducing agent and metal ions as required by claims 8 and 9.

Kidwell teaches that colloidal platinum may be used in a manner analogous to colloidal gold to immobilize proteins that bind to a target molecule present in a sample (column 4, lines 45-57 and column 7, lines 1-67).

Kidwell does not teach silver enhancement of the colloidal platinum.

Houthoff teaches that platinum may be conjugated (complexed) to biological molecules, such as proteins and nucleic acids, and used to detect the presence of a target molecule that binds to the platinum-immobilized biological molecule (column 2, lines 25-57 and column 4, lines 22-52). Houthoff further teaches that the platinum complexes of the invention can be used as a nucleation site for detection via silver enhancement using silver ions and a reducing agent, such as hydroquinone (column 12, line 66 – column 13, line 3 and column 24, line 64 – column 25, line 17).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize colloidal platinum or platinum complexes as the nucleation center-forming entities in the system resulting from the combined teachings of Mroczkowski and Hollis. As noted in MPEP 2144.06, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. In this case, as evidenced by the teachings of Kidwell and Houthoff, colloidal platinum and platinum complexes could be conjugated to biological molecules, such as proteins and nucleic acids, and used in

methods of detecting target biological molecules comprising silver enhancement that were analogous to the methods comprising the use of antibody-conjugated gold particles taught by Mroczkowski. Also, no evidence of unexpected results with respect to the use of platinum as the nucleation center-forming entity has been presented. Accordingly, an ordinary artisan would have been motivated to select this art-recognized equivalent for incorporation in the system resulting from the combined teachings of Mroczkowski and Hollis with a reasonable expectation of success. Thus, the systems of claims 8 and 9 are *prima facie* obvious in view of the combined teachings of the cited references.

14. Claims 35 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300; cited prevoiusly) in view of Olsen (US 5,614,832; cited previously).

Claim 35 is drawn to an electronic device for detecting a target biological molecule in a sample. Claim 41 is drawn to a method for using the electronic device of claim 35 to detect one or more targets in a sample.

Regarding claim 35, Mroczkowski teaches an electronic device for determining the presence or absence of one or more targets in a sample that comprises an integrated circuit having a first group of N1 conductors and a second group of N2 conductors, defining between them N1xN2 junctions, each junction being formed with an electronic module comprising two electrodes, wherein each electrode is linked to or defined as an integral portion of one of the conductors and supported by a common substrate, and wherein a current flowing between an N1 conductor and an N2 conductor defines a single junction point between the two conductors (see

Figure 8 and the accompanying description at page 17, lines 4-32). In the electronic device of Mroczkowski each pair of electrodes forms part of an assay set that comprises a recognition moiety that binds to a component of a cellular target and is immobilized on the substrate between the electrodes (see, for example, page 17, lines 7-12; see also page 5, lines 5-10 and page 10, lines 7-36 for further description of the recognition moieties). The electronic device of Mroczkowski also comprises a means for determining whether the one or more targets is present in the sample as a result of the extent of electric conductance between the two electrodes of each assay set (see page 17, line 33 – page 18, line 8, where the ohmmeter provides via the obtained resistance measurements an indirect measure of conductance, which is reciprocal ohms).

Finally, the assay sets in the device of Mroczkowski are adapted to accept reagents formulated to deposit a conductive substance onto a complex formed between a recognition moiety and a component of the cellular target (see pages 10 and 17, as discussed in greater detail above). It is noted that the limitations recited in lines 16-29 of the claim only require the electronic device to be **capable of** accepting the recited reagents and do **not** require the presence of the particular reagents recited in lines 16-29 of the claim to be present in the device. Since the device of Mroczkowski is designed to receive reagents (see page 10, for example), it is inherently adapted to receive the reagents described in lines 16-29 of claim 35.

Regarding claim 41, Mroczkowski teaches a method for detecting the presence or absence of one or more targets in a sample by multiplexing that comprises contacting a sample with the electronic device described above under conditions that permit binding of the one or more targets, if present in the sample, to the recognition moieties and determining the

conductance in each assay set (see page 17, line 4 – page 18, line 8; see also page 10, line 7 – page 11, line 4).

Mroczkowski does not teach that the disclosed integrated circuit further includes a diode that permits current flow through the electronic module only in the direction from the N1 conductors to the N2 conductors as required by claim 35.

However, as evidenced by Olsen (see, for example, the abstract, column 1, line 59 – column 2, line 13, Figure 1A, and column 2, lines 25-67), diodes were known in the art to be useful for regulating current flow between two electrodes such that current flow only occurs in a single user-selected direction. Olsen also teaches that the diodes permit the isolation of each circuit in a multi-circuit device from one another (column 2, line 35 – column 3, line 8) and further teaches that the disclosed diodes are useful for regulating voltage (column 3, lines 23-35).

Accordingly, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to further incorporate a diode into the integrated circuit taught by Mroczkowski. An ordinary artisan would have been motivated to do so in order to obtain a voltage regulating element and the ability to regulate the current flow between each pair of electrodes in the device of Mroczkowski such that current flow only occurs in a single user-selected direction. An ordinary artisan would have recognized from the teachings of Olsen that incorporation of diodes into the integrated circuits of Mroczkowski would have improved the circuits by electrically isolating each pair of electrodes from one another, and thereby, ensuring that the conductance measurements obtained for each circuit were independent. An ordinary artisan would have had a reasonable expectation of success in modifying the integrated circuit of Mroczkowski to further include a diode, since methods of constructing complex diode-

containing circuits were well-established in the art as evidenced by the teachings of Olsen. Thus, the electronic device of claim 35 and the method of claim 41 are *prima facie* obvious over Mroczkowski in view of Olsen.

15. Claims 36, 53, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300; cited prevoiusly) in view of Olsen (US 5,614,832; cited previously) and further in view of Hollis et al. (US 5,653,939; cited previously).

Claim 36 is drawn to the device of claim 35, wherein each of the assay sets in the device has a center that is separated from the center of an adjacent assay device by 100 μm or less. Claims 53 and 60 are drawn to the electronic device of claim 35, wherein the recognition moiety is a nucleic acid and the means for determining the presence of a target in the sample comprises a computer, respectively.

The combined teachings of Mroczkowski and Olsen render obvious the device of claim 35 and the method of claim 41, as discussed above.

Mroczkowski does not teach that the centers of the assay sets contained in the device are separated from the centers of adjacent assay sets by a distance within the range recited in claim 36. Mroczkowski also does not teach that the recognition moiety is a nucleic acid and the means for determining the presence of a target in the sample comprises a computer, as required by claims 53 and 60, respectively.

Hollis teaches methods and systems for detecting targets, including nucleic acids, proteins, antibodies, and cells, based on an observed change in an electrical signal resulting from the target binding to a recognition moiety immobilized to a substrate between two electrodes (see

abstract, Figure 4, Figure 22, and column 2, lines 25-52). The system of Hollis is similar to that of Mroczkowski in that it comprises: (i) a substrate upon which two electrodes are immobilized, a recognition moiety, which may be a protein, an antibody, or an oligonucleotide, immobilized on the substrate in the gap between the two electrodes, (ii), an electric or electronic module configured to measure electric conductance between the two electrodes, (iii) a sample, and (iv) a means for determining the presence of a target in the sample based on the extent of electric conductance between the electrodes (see column 4, lines 15-67, column 6, lines 10-26, column 7, lines 20-37, column 10, line 65 – column 11, line 10, and column 18, line 3 - column 19, line 15; see also Figures 4, 9, and 22). As discussed above, the combined teachings of Mroczkowski and Hollis render obvious the system of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65 and the methods of claims 24 and 47-49.

Regarding claim 36, Hollis teaches that the spacing between the centers of the test sites (*i.e.* assay sets) in the disclosed device is 4 microns, which lies within the claimed range (see, for example, column 6, lines 10-17).

Regarding claim 53, Hollis teaches that the disclosed system can be used to detect cellular, protein, or nucleic acid targets (see column 4, lines 21-25 and lines 41-45 and Table III at column 18). Hollis teaches that the detection of nucleic acid targets can be used in applications such as "genetic research, genetic and infectious disease diagnosis, toxicology testing, individual identification, agriculture identification and breed optimization, quality assurance through contaminant detection, and occupational hazard screening via mutation detection (column 16, lines 35-42)."

Regarding claim 60, Hollis teaches that "[T]he measurement process can be automated via on-chip microprocessor control to provide a very fast method of accessing each test site in the array (column 20, lines 14-16)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to apply the teachings of Hollis to the electronic device resulting from the combined teachings of Mroczkowski and Olsen. An ordinary artisan would have been motivated to select any known center-to-center spacing, such as the 4 micron spacing taught by Hollis, for the assay sets in the electronic device resulting from the combined teachings of Mroczkowski and Olsen, recognizing its suitability for the intended purpose. As noted in MPEP 2144.07, the selection of a known material or method based on its suitability for the intended purpose is *prima facie* obvious in the absence of unexpected results. In this case, since the devices taught by Mroczkowski and Hollis were directed to the same problem (*i.e.* array-based electrical detection of biological molecules) and possessed a similar structure, an ordinary artisan would have recognized that the center-to-center spacing taught by Hollis was suitable for use in the device resulting from the combined teachings of Mroczkowski and Olsen, and therefore, would have been motivated to select this known center-to-center spacing distance with a reasonable expectation of success. It is also noted that no evidence of unexpected results has been presented with respect to the spacing of the assay sets. An ordinary artisan also would have been motivated to utilize a nucleic acid as the recognition moiety in the device suggested by the combined teachings of Mroczkowski and Olsen. Since Hollis taught that nucleic acid detection could be used in numerous useful applications (column 16, lines 35-42), an ordinary artisan would have been motivated to adapt the device suggested by the combined teachings of

Mroczkowski and Olsen to the detection of these useful biological targets in order to maximize the number of useful applications of the system. An ordinary artisan would have had a reasonable expectation of success in doing so, since Mroczkowski taught that the method was not limited to any particular target, and Hollis taught that cells and nucleic acids were suitable targets for detection using electrical systems. Finally, an ordinary artisan would have been motivated to incorporate a computer as the means for determining the presence of a target in a sample in the system suggested by the combined teachings of Mroczkowski and Olsen. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Hollis taught that the electrical measurements in a similar system could be conducted using a computer to result in a rapid and automated detection step (column 20, lines 14-16). Thus, the systems of claims 36, 53, and 60 are *prima facie* obvious over Mroczkowski in view of Olsen and further in view of Hollis.

16. Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300; cited prevoiusly) in view of Olsen (US 5,614,832; cited previously) and further in view of Hollis et al. (US 5,653,939; cited previously).

Claims 38 and 39 are drawn to the system of claim 18 and the method of claim 24, respectively, and further limit the structure of the assay device.

As discussed above, the combined teachings of Mroczkowski and Hollis render obvious the systems of claims 1, 4-7, 18-20, 22, 23, 43, 44, 55, 57, and 65 and the methods of claims 24 and 47-49.

Regarding claims 38 and 39, Mroczkowski teaches an electronic device for determining the presence or absence of one or more targets in a sample that comprises an integrated circuit having a first group of N1 conductors and a second group of N2 conductors, defining between them N1xN2 junctions, each junction being formed with an electronic module comprising two electrodes, wherein each electrode is linked to or defined as an integral portion of one of the conductors and supported by a common substrate, and wherein a current flowing between an N1 conductor and an N2 conductor defines a single junction point between the two conductors (see Figure 8 and the accompanying description at page 17, lines 4-32). Mroczkowski also teaches using the disclosed electronic device to detect the presence or absence of one or more targets in a sample (see page 17, line 4 – page 18, line 8; see also page 10, line 7 – page 11, line 4).

Neither Mroczkowski nor Hollis teaches that the disclosed electronic device further includes a diode as required by claims 38 and 39.

However, as evidenced by Olsen (see, for example, the abstract, column 1, line 59 – column 2, line 13, Figure 1A, and column 2, lines 25-67), diodes were known in the art to be useful for regulating current flow between two electrodes such that current flow only occurs in a single user-selected direction. Olsen also teaches that the diodes permit the isolation of each circuit in a multi-circuit device from one another (column 2, line 35 – column 3, line 8) and further teaches that the disclosed diodes are useful for regulating voltage (column 3, lines 23-35).

Accordingly, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to further incorporate a diode into the integrated circuit taught by Mroczkowski. An ordinary artisan would have been motivated to do so in order to obtain a voltage regulating element and the ability to regulate the current flow between each pair of

electrodes in the device of Mroczkowski such that current flow only occurs in a single user-selected direction. An ordinary artisan would have recognized from the teachings of Olsen that incorporation of diodes into the integrated circuits of Mroczkowski would have improved the circuits by electrically isolating each pair of electrodes from one another, and thereby, ensuring that the conductance measurements obtained for each circuit were independent. An ordinary artisan would have had a reasonable expectation of success in modifying the integrated circuit of Mroczkowski to further include a diode, since methods of constructing complex diode-containing circuits were well-established in the art as evidenced by the teachings of Olsen. Thus, the system of claim 38 and the method of claim 39 are *prima facie* obvious in view of the combined teachings of the cited references.

17. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Hollis et al. (US 5,653,939; cited previously) and further in view of Althainz et al. (Sensors and Actuators B (1996) 33(1-3): 72-76; newly cited).

Claim 56 is drawn to the system of claim 1, wherein the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner.

As discussed above, the combined teachings of Mroczkowski and Hollis render obvious the system of claims 1, 4-7, 18-20, 22, 23, 43, 44, 54, 55, 57, 62, and 65 and the methods of claims 24 and 47-49.

Neither Mroczkowski nor Hollis teaches that the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device is a scanner as required by claim 56.

However, as evidenced by Althainz (see pages 72-73), scanners were known in the art to be useful as part of a means for indirectly measuring conductance at each site in a microsensor array comprising a plurality of electrodes via the measurement of resistance.

Accordingly, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate a scanner in the system resulting from the combined teachings of Mroczkowski and Hollis as part of the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device. As noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, as evidenced by the teachings of Althainz, a scanner was known in the art to be suitable for use as a component of in a means for obtaining array-based conductance measurements. Also, no evidence of unexpected results with respect to the use of a scanner has been presented. Accordingly, an ordinary artisan would have been motivated to select this known element for incorporation in the system resulting from the combined teachings of Mroczkowski and Hollis with a reasonable expectation of success. Thus, the system of claim 56 is *prima facie* obvious in view of the combined teachings of the cited references.

18. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Olsen (US 5,614,832; cited previously) and further in view of Althainz et al. (Sensors and Actuators B (1996) 33(1-3): 72-76; newly cited).

Claim 61 is drawn to the device of claim 35, wherein the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner.

As discussed above, the combined teachings of Mroczkowski and Olsen render obvious the device of claim 35 and the method of claim 41.

Neither Mroczkowski nor Olsen teaches that the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner as required by claim 61.

However, as evidenced by Althainz (see pages 72-73), scanners were known in the art to be useful as part of a means for indirectly measuring conductance at each site in a microsensor array comprising a plurality of electrodes via the measurement of resistance.

Accordingly, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate a scanner in the device resulting from the combined teachings of Mroczkowski and Olsen as part of the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device. As noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, as evidenced by the teachings of Althainz, a scanner was known in the art to be suitable for use as a component of a means for obtaining array-based conductance measurements. Also, no

evidence of unexpected results with respect to the use of a scanner has been presented. Accordingly, an ordinary artisan would have been motivated to select this known element for incorporation in the device resulting from the combined teachings of Mroczkowski and Olsen with a reasonable expectation of success. Thus, the device of claim 61 is *prima facie* obvious in view of the combined teachings of the cited references.

19. Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski et al. (WO 90/05300 A1; cited previously) in view of Althainz et al. (Sensors and Actuators B (1996) 33(1-3): 72-76; newly cited).

Claim 63 is drawn to the device of claim 37, wherein the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner.

As discussed above, Mroczkowski teaches the device of claim 35.

Mroczkowski does not teach that the means for determining the presence of a target in a sample based on the extent of conductance between each pair of electrodes in the assay device comprises a scanner as required by claim 63.

However, as evidenced by Althainz (see pages 72-73), scanners were known in the art to be useful as part of a means for indirectly measuring conductance at each site in a microsensor array comprising a plurality of electrodes via the measurement of resistance.

Accordingly, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate a scanner in the device of Mroczkowski as part of the means for determining the presence of a target in a sample based on the extent of conductance between

each pair of electrodes in the assay device. As noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, as evidenced by the teachings of Althainz, a scanner was known in the art to be suitable for use as a component of a means for obtaining array-based conductance measurements. Also, no evidence of unexpected results with respect to the use of a scanner has been presented. Accordingly, an ordinary artisan would have been motivated to select this known element for incorporation in the device of Mroczkowski with a reasonable expectation of success. Thus, the device of claim 63 is *prima facie* obvious in view of the combined teachings of the cited references.

Response to Arguments

20. In view of the claim amendments, the rejection of claims 1, 4-9, 18-20, 22, 23, and 57 under 35 U.S.C. 102(b) as being anticipated by Mroczkowski has been withdrawn. Also, the previously made rejection of claim 27 under 35 U.S.C. 102(b) as being anticipated by Mroczkowski has been withdrawn in view of the cancellation of this claim. However, as discussed above, claims 25, 26, 28, 37, 50, and 51 have been rejected under 35 U.S.C. 102(b) as being anticipated by Mroczkowski. Applicant's arguments filed on October 28, 2009 remain pertinent to the new grounds of rejection above. These arguments have been fully considered, and they were persuasive, in part.

Applicant first argues that Mroczkowski does not teach all of the elements of the rejected claims as amended. Specifically, Applicant argues that Mroczkowski does not teach that the recognition moieties form complexes with a component of the targets, which are selected from

the group consisting of a cell, a bacterium and a virus, whereas the nucleation center-forming entities are capable of binding to one or more targets (pages 20-21). This argument was persuasive with respect to independent claim 1, and accordingly, claims 1, 4-9, 18-20, 22, 23, and 57 have not been rejected under 35 U.S.C. 102(b) as being anticipated by Mroczkowski. This argument was not persuasive, with respect to independent claims 25, 26, and 28, however. Unlike claim 1, these claims do not require that the recognition moiety binds to a component of a virus, bacterium, or cell, whereas the nucleation center-forming entity binds to the bacterium, virus, or cell. Rather, claims 25, 26, and 28 require the recognition moiety and the nucleation center-forming entity to be capable of binding specifically to a biological molecule target. As discussed above, the recognition moieties and nucleation center-forming entities of Mroczkowski possess the required functional properties.

It is also noted that the claims do not require that the nucleation center-forming entity to be capable of binding more than one biological target molecule as argued by Applicant at pages 21-22. Claims 25, 26, and 28 only require the nucleation center-forming entity to bind to **one or more** biological target molecules. As discussed above, the nucleation center-forming entities (*i.e.* the gold-labeled antibodies) disclosed by Mroczkowski bind to at least one biological target molecule (see page 10), and therefore, they meet the requirements of the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Also, in contrast to Applicant's arguments at pages 21-22, the nucleation center-forming entities in Mroczkowski bind only when the biological molecule target is present, since their binding

depends on specific binding between the antibody component of the entity and the biological target molecule.

It is further noted that, in contrast to Applicant's arguments at pages 22-23, the language of claims 25, 26, and 28 does not exclude nucleation center-forming entities, such as those disclosed by Mroczkowski, in which the nucleation center-forming entity (*i.e.* the gold particle) is conjugated to another material, such as an antibody, thereby resulting in indirect binding of the nucleation center-forming entity to the biological target molecule. Claims 25, 26, and 28 only require the sample to be reacted with a reagent solution to bind nucleation center-forming entities to the biological targets, and therefore, these claims do not exclude indirect binding of the gold particles to the biological targets via the antibody as argued by Applicant at pages 22-23. Neither the claim language nor an explicit and limiting definition in the specification prohibits conjugation of the nucleation center-forming entity to another molecule, such a second recognition moiety in the form of an antibody. Rather, the definition provided on page 6 of the specification expressly states that the nucleation center-forming entities may be conjugated to a target-binding molecule. Further, as noted above, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Since Applicant's arguments were not persuasive, claims 25, 26, 28, 37, 50, and 51 have been rejected under 35 U.S.C. 102(b) as being anticipated by Mroczkowski.

Applicant's arguments filed on October 28, 2009, regarding the previously made rejections of claims 24, 43-45, 47-51, 55, 56, and 65 under 35 U.S.C. 103(a) citing Mroczkowski as the primary reference, also remain pertinent to the new grounds of rejection made above.

These arguments have been fully considered, but they were not persuasive. In view of the claim amendments, claims 1, 4-9, 18-20, 22-24, 35, 41, 43, 44, 47-49, 54-57, 61-63, and 65 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Mroczkowski in view of various secondary references.

Applicant argues that the teachings of the secondary references do not remedy the deficiencies of the Mroczkowski reference discussed with respect to the rejection made under 35 U.S.C. 102(b) (see pages 23-24). This argument was not persuasive, because as discussed above, the combined teachings of Mroczkowski and the cited secondary references suggest all of the elements of the rejected claims.

Since Applicant's arguments were not persuasive, the rejections have been maintained with modifications to address the claim amendments.

Conclusion

21. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Angela M Bertagna/
Examiner, Art Unit 1637